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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41 and 94-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41 and 94-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/19/09 has been entered.

The amendment, declaration of Dr. Patrick Hwu and remarks filed 1/19/09 are acknowledged. Claim 41 has been amended. Claims 41, 94-111 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 1/19/09 response would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 41 is objected to because it encompasses more than one invention as defined in the Restriction requirement mailed 7/8/02. Specifically, the elected invention of group I is directed to dual specific lymphocytes and an *ex vivo* method of preparing such (see original claim 41). During the prosecution of the application, claim 41 has been amended to the current form that reads on both *ex vivo* and *in vivo* methods. Upon

election of an invention for examination, said claim should only reads upon the elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 94-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

At issue for written description in the instant case are:

a). Claims are inclusive of a genus of "mixed population of cells". Claims are directed to a method of preparing dual specificity lymphocytes, claim 41 recites contacting lymphocytes "in a mixed population of cells", which embraces any mixed population of cells that contain lymphocytes. However, the only mixed populations of cells disclosed in the specification are tumor infiltrating lymphocytes or T lymphocytes. The specification fails to teach any other mixed cell population suitable for use in the instantly claimed invention.

b). Claims are inclusive of a genus of cells allogeneic to one or more lymphocytes, which embrace any cell type known to exist. However, the only allogeneic cells capable of stimulating lymphocytes are antigen-presenting cells as listed for example, in figure 13, i.e. dendritic cells (DCs), B lymphocytes, and PBMCs which include DCs and B cells. The specification fails to teach any other allogeneic cells capable of select and specifically amplify lymphocytes.

c). Claims are inclusive of a genus of endogenous receptors that are reactive with an allogeneic cell. However, beyond a T cell receptor, the specification fails to teach another "endogenous" receptor that perform the function and suitable for use in the instantly claimed invention. The specification fails to provide an adequate description for the genus of endogenous receptors as claimed.

d). Claims are inclusive of a genus of "chimeric receptor" reactive with a tumor antigen. However, the only type of chimeric receptor disclosed in the specification is a fusion receptor between a single chain antibody that recognizes a tumor antigen and a

T cell receptor capable of triggering T cell signal transduction. The specification fails to provide an adequate description for the genus of chimeric receptors as claimed

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A DESCRIPTION OF A GENUS OF cDNAs MAY BE ACHIEVED BY MEANS OF A RECITATION OF A REPRESENTATIVE NUMBER OF cDNA, DEFINED BY NUCLEOTIDE SEQUENCE, FALLING WITHIN THE SCOPE OF THE GENUS OR OF A RECITATION OF STRUCTURAL FEATURES COMMON TO THE MEMBERS OF THE GENUS, WHICH FEATURES CONSTITUTE A SUBSTANTIAL PORTION OF THE GENUS." In regards to a genus defined by function, without a correlation between structure and function, the claim does little more than define the genus by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly, 119 at1568 USPQ2d at 1406* ("DEFINITION BY FUNCTION…DOES NOT SUFFICE TO DEFINE THE GENUS BECAUSE IT IS ONLY AN INDICATION OF WHAT THE GENE DOES, RATHER THAN WHAT IT IS"). The inventions at issue in Lilly were DNA constructs per se, the holdings of that case is also applicable to claims such as those at issue here. Further, disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient

descriptive information, such as consensus structural or functional features that are common to the genus. That is, the specification provides neither a representative number of "chimeric receptors" or "endogenous receptors", for example, that encompass the genus nor does it provide a description of structural features that are common to the genus. Since except the recited combination acknowledged *supra*, the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of the specification is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

The MPEP states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED WHERE AN INVENTION IS DESCRIBED SOLELY IN TERMS OF A METHOD OF ITS MAKING COUPLED WITH ITS FUNCTION AND THERE IS NO DESCRIBED OR ART-RECOGNIZED CORRELATION OR RELATIONSHIP BETWEEN THE STRUCTURE OF THE INVENTION AND ITS FUNCTION" (MPEP 2163 I-A). "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS" (MPEP 2163.05), "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (MPEP 2163 II).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope Therefore, only the described lymphocytes, allogeneic antigen presenting cells, chimeric Ab/TCR and endogenous TCR meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 41, 94-111 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to

the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

As indicated *supra* in the written description section, the specification fails to provide an adequate description for the genus of mixed cell populations, the genus of cells allogeneic to T lymphocytes, the genus of chimeric receptors and the genus of endogenous receptors of lymphocytes. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, the description alone is insufficient to describe the genus.

Although the claims broadly encompass preparing any type of dual specific lymphocytes, since the selection and amplification depend on T cell receptors, the end product could only be T lymphocytes.

With respect to the function of selecting and specifically amplifying lymphocytes comprising a TCR reactive with a specific allogeneic cell, the knowledge of the art is such that the function is specialized between antigen presenting cells and T lymphocytes, i.e. only antigen-presenting cells are capable of reacting with TCR on the surface of T lymphocytes and *vice versa* (see e.g. figure 5.17 and Part II, ¶ 5, *Janeway et al*., Immunobiology 2001). It was not known and the specification fails to teach any mixed cell population and any allogenic cell would perform the recited function.

The specification also fails to teach in the case of a mixed cell population, how to isolate the desired lymphocytes from mixed cell types. Accordingly, the specification fails to provide an enabling disclosure for what is now claimed.

Accordingly, in view of the limited guidance, the knowledge of the skilled in the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41, 94-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, “a mixed population of cells". The specification fails to define the term, it is unclear what “mixed” embraces or excludes. For example, a population of different types of cells, or a population of T lymphocytes with different TCR receptors. Thus, the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 94-103, 105, 106, 108-111 stand rejected under 35 U.S.C. 103(a) as being obvious over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34), for reasons of record and following.

Hwu et al. teaches a method for preparing tumor reactive lymphocytes comprising **a**). providing murine tumor infiltrating lymphocytes (TIL) transduced with a recombinant retroviral vector encoding a chimeric Ab/TCR receptor (Mov-γ) reactive with ovarian adenocarcinoma cells in the presence of IL-2 (e.g. the abstract, and column 2, page 3369), wherein the chimeric receptor comprising a single chain variable region from mAbs joined to the Fc receptor γ chain and capable of mediating T cell receptor signal transduction and binding FBP (e.g. column 2, page 3369), and **b**). the transduced TIL cells were co-cultured with syngeneic MC38 colon tumor cells, which results in a large amount of mIFN-γ production (indicating the TIL cells contain an endogenous T-cell receptor reactive with the syngeneic MC38 cells). The process taught by *Hwu et al* differs from instantly claimed in that the (stimulator) tumor cell in the co-culture is syngenic, not allogenic.

Munz et al. supplemented *Hwu et al.* by establishing that using an allogenic cell as T cell stimulus is comparable to the syngenic/autologous stimulation in obtaining potent tumor reactive CTL cells. *Munz et al.* co-cultured PBL with irradiated allogenic

(T2 cells) or syngenic PBL in the presence of IL-2 (left column, page 26), and reported that allogenic APC allows the stimulation of high avidity cytotoxic T cell. *Munz et al.* also taught the need in the art for the allorestricted T cells because the immune system of a cancer patient is often partially destroyed by chemotherapy or factors produced by tumor cells, and under such circumstance, allogenic APCs may be used for tumor antigen-specific T cell activation in immunosuppressed patients (e.g. the paragraph bridging pages 32-33), and concluded with respect to allogenic stimulated T lymphocytes, "SUCH T CELLS MIGHT INDEED BE USEFUL FOR TUMOR IMMUNOTHERAPY" (e.g. abstract). *Munz* also teaches that the method allows the stimulation of high avidity cytotoxic T cells (e.g. the abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the preparation process as taught by *Hwu et al.,* with that of *Munz et al.* by co-culturing either syngenic or allogenic APCs with T cells for activation and expansion, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit as taught by *Munz et al*. Given numerous methods known in the art for T cell activation and expansion, this limitation falls within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The remarks are based on the declaration of Dr. Hwu, and cited three post-filing publications, which will be addressed following:

In section 6 of the declaration, the applicant argues that successfully generating a potent immune response against a tumor antigen using dual specific T cells is difficult and at best unpredictable because T cells expressing two receptors can exhibit cross-antagonism, citing *Yang et al*. for support.

The argument and reference have been fully considered but found not sufficient to obviate instant rejection. As an initial matter, it is noted that the instant claims are directed to an *in vitro* method of preparing dual specific T cells, not a method for generating a potent immune response against a tumor antigen *in vivo*. The TCR antagonism occurs when one TCR *antagonist* interfere with another TCR during an immune response. This is highly unlikely in the instant case wherein the structure of the alloreactive TCR and the chimeric tumor-specific receptor are remarkably different for an antagonist to exist. Further, the step of allogeneic reaction occurs before or separate from the transducing with the chimeric receptor, therefore, no interference is likely to happen in the absence of evidence to the contrary. Last but not the least, the teaching of *Hwu* reference provides that the dual reactive T cells are not concerned with TCR antagonism.

In section 7 of the declaration, the applicant argues one of ordinary skill in the art would not have been led to modify the procedure described because the potency of the

alloreactive response is so strong, the alloreactive response commandeers the internal machinery of the cell.

The argument has been fully considered but found not persuasive. This is because *Munz et al.* established that for in an *ex vivo* activation and expansion process, using an allogeneic cell as T cell stimulus is comparable to the syngenic/autologous stimulation in obtaining potent tumor reactive CTL cells, and the reaction does not take over the internal machinery of the lymphocytes, rather, it produces high avidity CTLs.

In section 8 of the declaration, the applicant points to example 1 of the specification, showing T cells prepared by a method encompassed by the instant claims failed to effectively treat cancer.

The argument has been fully considered but found not persuasive. The reference cited in example 1 of the specification is the reference cited in the base of the instant rejection (Hwu et al. Cancer Res. 1995). Again, instant claims are not directed to a method for inducing potent anti-tumor immune response in a patient, but methods for preparing dual reactive T cells *in vitro*. Although the applicant acknowledges the T cells were insufficient to treat cancer in patients in the specification, this was not taught or known in the art. *Assuming arguendo* that the fact was known in the art, it would have motivated the skilled in the art to further improve the method of preparation such as taught by *Munz* so that a more potent T cells could be prepared. Further, *Munz* teaches the need in the art for preparing the allorestricted T cells because the immune system of a cancer patient is often partially destroyed by chemotherapy or factors produced by

tumor cells, and under such circumstance, allogeneic APCs may be used for tumor antigen-specific T cell activation in immunosuppressed patients.

Sections 9-12 teaches the success of T cells in fighting cancer prepared by instantly claimed method.

In response, it is noted instant claims are directed to a method of preparing cells and the celled obtained. As long as there is a reasonable motivation to do so, the combined teaching of the prior art would render the process unpatentable even though they may not have the same motivation to perform the process.

As to the two post-filing publications co-authored by instant applicant, it is noted they reflect further development in the pertinent art since the filing of instantly claimed invention. For example, the *Kershaw* reference designs a dual-specific T cells that could be sustained *in vivo* when incorporated with an immunization regimen.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claim 104 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34) as applied to claims 41, 94-103, 105, 106, 108-111 above, and further in view of *Kawakami et al* (USP 5,844,075), for reasons of record and set forth *supra*.

Claim 107 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol

1999;162:25-34) as applied to claims 41, 94-103, 105, 106, 108-111 above, and further in view of *Raubitschek et al* (USP 6,41,319), for reasons of record and set forth *supra*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is 571-272-0730. The examiner can normally be reached on 9 AM -7:00pm, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633